International Journal of Infectious Diseases 17 (2013) e185–e188

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Standardized outpatient management of *Klebsiella pneumoniae* liver abscesses

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ARTICLE INFO

Article history:
Received 5 April 2012
Accepted 17 October 2012

Corresponding Editor: Meinolf Karthaus, Munich, Germany

Keywords:
Klebsiella
Liver
Abscess
Outpatient
Antibiotic

SUMMARY

Objectives: Community-acquired *Klebsiella pneumoniae* has emerged as a major cause of liver abscess in Asia. Using a standardized protocol, we conducted a prospective cohort study of all cases of *K. pneumoniae* liver abscess treated from 2005 to 2011 at two outpatient parenteral antimicrobial therapy (OPAT) centers in Singapore, to assess the safety and efficacy of treatment.

Methods: We included all OPAT eligible patients with radiologically confirmed (computed tomography or ultrasound) liver abscesses and *K. pneumoniae*-positive microbiological cultures obtained from abscess fluid and/or blood at two university teaching hospitals. The endpoints investigated were cure, clinical response, readmission, and mortality.

Results: All 109 patients enrolled in the study successfully completed treatment in OPAT. Nine patients required a short-term readmission due to clinical deterioration. There were no deaths or relapses at 30 days post cessation of antibiotics. Abscess size greater than 5 cm was associated with a delayed clinical response (odds ratio 5.34, 95% confidence interval 1.25–22.91, $p = 0.02$).

Conclusion: The management of *K. pneumoniae* liver abscesses via OPAT using a standardized protocol is a safe and effective alternative to inpatient intravenous antibiotics.

1. Introduction

Pyogenic liver abscess is a condition with mortality rates ranging from 11% to 31%.[1] It may be caused by a number of organisms including *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus anginosus*, and anaerobes such as *Bacteroides* species.[2] In the last 20 years, community-acquired pyogenic liver abscess caused by *K. pneumoniae* has emerged in Taiwan and other Asian countries as a unique entity. In particular, the hypermucoid K1 and K2 capsular serotypes have been found to be associated with metastatic infections and more severe disease.[3] In Singapore, *K. pneumoniae* is the most common organism isolated in patients with pyogenic liver abscess.[4]

The management of liver abscesses involves a combination of antimicrobials to which the offending organism is susceptible and drainage where indicated. Radiologically guided percutaneous aspiration has in many cases replaced surgical drainage, resulting in shorter hospital stays and fewer complications.[5]

The antibiotic treatment for pyogenic liver abscesses usually involves 2 to 3 weeks of parenteral administration followed by oral antibiotics to complete a total 4- to 6-week course.[2,6] The availability of outpatient parenteral antimicrobial therapy (OPAT) services potentially allows patients to have their parenteral antibiotics administered out of the hospital for at least part of the course.

We conducted a prospective cohort study examining the safety and efficacy as well as risk factors for a poor clinical response in *K. pneumoniae* liver abscess (KLA) cases treated via OPAT in Singapore.

2. Materials and methods

2.1. Study sites

The National University Hospital (NUH) and Tan Tock Seng Hospital (TTSH) are university teaching hospitals with OPAT centers catering to patients requiring intravenous antibiotic therapy. The two centers provide the majority of OPAT services in Singapore, enrolling an average of 500 patients per year (794 and 706 patients, respectively, in the last 3 years). Consecutive cases of KLA treated via OPAT at NUH and TTSH from January 2005 to July 2011 were enrolled and monitored prospectively.

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1201-9712/$36.00 – see front matter
http://dx.doi.org/10.1016/j.ijid.2012.10.002

2.2. Participants

Patients were enrolled into the OPAT service after being assessed by an infectious diseases physician and an OPAT specialist nurse. To be eligible, patients had to have an infection requiring intravenous antibiotics that were appropriate for OPAT administration, venous access, and social circumstances deemed safe. Our inclusion criteria were OPAT eligible patients with radiologically confirmed (computed tomography or ultrasound) liver abscesses and *K. pneumoniae*-positive microbiological cultures obtained from abscess fluid and/or blood.

Patients with non-*K. pneumoniae* liver abscesses were excluded from the analysis. The choice of antibiotic was based on the susceptibility profiles reported by the microbiology laboratory of each hospital.

2.3. Study procedures

Patients were managed using a standardized protocol: (1) daily clinical nursing review to assess for any adverse events; (2) weekly physician review of clinical features and laboratory parameters including full blood count, liver function tests, electrolytes, creatinine, and C-reactive protein (CRP); (3) repeat imaging of liver abscesses with either ultrasound or computed tomography prior to antibiotic cessation or conversion to oral therapy.

2.4. Microbiology

The identification and susceptibility testing of *K. pneumoniae* isolates were performed using the VITEK 2 system (bioMérieux) at NUH during the entire duration of the study. At TTSH, organism identification was performed using a mix of Microbact™ 12A (Oxoid, UK), VITEK 2 system (bioMérieux), and the Bruker Biotyper (version 2.0) matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry system; susceptibility testing was performed using the VITEK 2 system (bioMérieux) and Kirby–Bauer method. At NUH, interpretation of susceptibility was based on the Clinical and Laboratory Standards Institute (CLSI) breakpoints from 2005 to 2009, after which the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used. At TTSH, CLSI breakpoints were used during the entire duration of the study.

2.5. Study outcomes

Our endpoints were cure, clinical response, readmission, and mortality. Cure was defined as the absence of symptoms, normalization of CRP (<10 mg/l), radiologic resolution, and no signs of relapse at 30 days post cessation of antibiotics. Clinical response was defined as resolution of symptoms with normalization of CRP to <10 mg/l at 4 weeks of therapy. Readmission was defined as an admission from OPAT to hospital while still receiving antimicrobial therapy for KLA. Mortality was defined as death during OPAT therapy or within 30 days of cessation of antibiotics.

2.6. Data collection

The two OPAT services shared a common prospective OPAT database to record patient demographics (age, gender), microbiology and site of infection, antibiotic selection and duration, type of intravenous access, and mode of administration. Medical and laboratory records provided additional data on co-morbidities, antibiotic susceptibility, radiological findings (size of abscess and presence of loculations), laboratory results (white blood cell count, liver function tests, CRP), and any intervention including percutaneous or surgical drainage. Other data collected included length of hospital stay before discharge to OPAT and length of OPAT.

Table 1
Patient demographics ($n = 109$)

Variable	Finding
Male sex	72
Age, years, mean ± SD (range)	57 ± 13 (26–83)
Co-morbidities, *n* (%)	
Diabetes	49 (45%)
Hypertension	48 (44%)
Renal impairment	6 (6%)
Ischemic heart disease	6 (6%)
Hyperlipidemia	30 (28%)
Underlying malignancy	13 (12%)

SD, standard deviation.

2.7. Statistical analysis

All statistical analyses were performed using SPSS 18.0 (PASW). Associations of the categorical variables with readmission and clinical response were assessed using the Chi-square/Fisher's exact test and logistic regression for multivariate analysis. Odds ratios (OR) and their 95% confidence intervals (CI) were presented, with statistical significance set at $p < 0.05$.

3. Results

Of 205 patients with pyogenic liver abscess treated in the two OPAT centers between January 2005 and July 2011, 109 had KLA and were included in the study (Table 1). Seventy-two (66%) were male and the mean age was 57 years (standard deviation (SD) 13). *K. pneumoniae* was identified from blood cultures in 71 (65%) patients and liver abscess fluid only in 38 (35%) patients. Of the blood culture-positive cases, 32 had *K. pneumoniae* also isolated in the liver abscess. Two of the patients who underwent aspiration/surgical drainage were culture-negative despite being bacteremic. The size of the liver abscesses was greater than 5 cm in 71 patients (65%). The mean length of hospital stay was 15 days (SD 10), while the mean length of OPAT management was 16 days (SD 9) (Table 2).

Surgical drainage was undertaken in seven patients and radiologically guided drainage in 65 patients. Drainage was deemed inappropriate in 37 patients (34%) due to the radiologic appearance of the abscess.

Of 71 patients with abscesses greater than 5 cm in diameter, 60 (85%) were treated with drainage and antibiotics while the remainder received antibiotics alone. Twenty-six of the 38 patients (68%) with abscesses less than 5 cm in diameter had antibiotic treatment alone. Antibiotics were selected based on the susceptibility patterns of *K. pneumoniae* reported by the microbiology laboratories. In no instance was antibiotic use discordant with the antimicrobial susceptibility of the organism. Ceftriaxone was most commonly used (71 cases, 65%), while cefazolin was given to 24

Table 2
Patient outcomes

Variable	Mean ± SD (range)
Length of hospital stay, days	15 ± 10 (3–84)
Length of OPAT administered antibiotics	16 ± 9 (2–54)
Delayed clinical response at 4 weeks, *n*	29
Readmission from OPAT during parenteral therapy, *n*	9
Total duration of IV therapy, days	32 ± 13 (11–98)
Duration of subsequent oral therapy, days	42 ± 26 (7–140)

SD, standard deviation; OPAT, outpatient parenteral antimicrobial therapy; IV, intravenous.

Table 3
Variables associated with a poor outcome

Variables	Lack of clinical response at 4 weeks			Readmission		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age >60 years	1.46	0.52–4.09	0.47	3.05	0.34–27.57	0.32
Male sex	0.72	0.26–1.98	0.52	0.29	0.03–2.66	0.28
Diabetic	1.13	0.42–3.04	0.81	0.55	0.05–6.22	0.63
Bacteremia	1.16	0.40–3.35	0.78	9.83	0.65–149.0	0.10
Abscess size >5 cm	5.34	1.25–22.91	0.02	2.40	0.16–37.02	0.53
Loculation	0.52	0.14–1.87	0.31	N/A	N/A	N/A
Percutaneous drain	0.82	0.25–2.71	0.74	10.0	0.51–195.11	0.13

OR, odds ratio; CI, confidence interval; N/A, not applicable.

patients, ertapenem to 11, meropenem to two, and amikacin to one. Comparing cefazolin and ceftriaxone treatment, there was no difference in clinical response or readmission from OPAT to hospital.

Eighty patients achieved a clinical response at 4 weeks. A delayed clinical response (i.e., patient still symptomatic and/or CRP >10 mg/l at 4 weeks of therapy) was noted in 29 patients (27%) (Table 2). This was associated with abscess size greater than 5 cm in diameter (Table 3) (OR 5.34, 95% CI 1.25–22.91; $p = 0.02$). Nine patients were readmitted from OPAT, three for surgical drainage after failing initial percutaneous drainage of their liver abscesses, five for worsening of underlying non-infectious co-morbidities, and one for an infectious condition unrelated to the KLA. All patients in the study achieved cure, with no deaths or relapses at 30 days post cessation of antibiotics, including the nine readmissions who subsequently completed OPAT.

4. Discussion

Except for a delayed clinical response at 4 weeks in patients with liver abscesses greater than 5 cm in size, our study found no differences in the outcomes of patients with KLA managed in OPAT across a range of host, disease, and treatment factors (Table 3).

The age of patients with *K. pneumoniae* liver abscesses in previous studies has ranged from 55 to 60 years.[7] The mean age of our cohort of patients was 57 years. Older age may or may not be associated with increased mortality.[8,9] We found no differences in clinical response or readmission rates in patients older than 60 years.

Diabetes mellitus is a known risk factor for the development of *K. pneumoniae* liver abscess and was overrepresented in our cohort (45%). We found that the presence of diabetes mellitus was not associated with a poor clinical response or increased risk of readmission. This supports the findings of Lee et al., who reported no association between diabetes mellitus and severe disease or death.[10] Diabetes has, however, been identified as a risk factor for metastatic complications.[11]

We did not find any differences in clinical response or readmission from OPAT to hospital between patients on cefazolin and those on ceftriaxone. In their study comparing the use of cefazolin versus an extended-spectrum cephalosporin for treating KLA, Cheng et al. found a significantly higher complication rate in patients treated with cefazolin. They hypothesized that this could be due to inoculum-dependent inactivation of the antibiotic by chromosomally mediated SHV-1 beta-lactamases, which are expressed by all strains of *K. pneumoniae*.[6] However in their retrospective analysis of 110 episodes of KLAs, Lee et al. concluded that the use of first-generation cephalosporins and percutaneous drainage was associated with low rates of mortality, metastatic infection, and complications, and that these rates were comparable to those reported for third-generation cephalosporins.[10]

Liver abscesses greater than 5 cm in diameter had a higher rate of treatment failure if treated medically alone.[12] Large abscesses have been found to be a poor prognostic indicator for mortality.[13] In our cohort of patients, 85% of liver abscesses that were greater than 5 cm in diameter were subject to either radiologically guided percutaneous aspiration ($n = 53$) or open/laparoscopic surgical drainage ($n = 7$). Patients with abscesses larger than 5 cm in diameter had a delay in clinical response. However this was not associated with an increased risk of readmission or mortality.

None of the 37 patients who were treated medically alone required readmission or incurred any other adverse outcome post discharge. Furthermore they trended towards shorter total treatment courses (mean duration of 63 ± 29 days versus 72 ± 31 days in those with drainage). The fact that up to two-thirds of these patients had smaller abscesses that could be treated successfully with medical therapy alone may account for this. The presence of loculations within the abscess was not associated with a worse outcome, reinforcing the findings of previous studies that have shown percutaneous drainage to be a safe and effective procedure in treating pyogenic liver abscess regardless of abscess complexity and/or multiplicity.[14]

There were nine patients readmitted from OPAT. Three were readmitted for surgical drainage after failing initial percutaneous drainage and all of them had abscesses greater than 5 cm in diameter. In a series of 80 patients, Tan et al. found that for liver abscesses larger than 5 cm, surgical drainage resulted in better outcomes than percutaneous drainage in terms of treatment success and the necessity for secondary procedures.[15]

K. pneumoniae liver abscesses can be managed effectively and safely via OPAT in situations where guidelines are in place for reducing the clinical risk by draining pus when abscesses are large (i.e., greater than 5 cm), administering appropriate antibiotics based on the susceptibility profile of the organism, and monitoring patients clinically using a standardized protocol.

Acknowledgements

We would like to acknowledge Dr Timothy Barkham for his assistance with the microbiological methods at TTSH and Dr Chan Yiong Huak for his assistance with the statistical analysis.

Ethical approval: This study was given ethical approval by the National Health Group Domain specific review board.

Funding: No funding was received for this study

Conflict of interest: No conflict of interest to declare.

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